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(54) Title: A SYNERGISTIC PHARMACEUTICAL COMBINATION COMPRISING CICLETANINE FOR THE PREVENTION OR TREATMENT OF DIABETES

(57) Abstract: The invention refers to a synergistic pharmaceutical combination which comprises (a) a first pharmaceutical composition containing cicletanine or a pharmaceutically suitable acid addition salt thereof and one or more conventional carrier(s), and (b) a second pharmaceutical composition containing an antidiabetic or anti-hyperlipidemic active agent or, if desired and chemically possible, a pharmaceutically suitable acid addition salt or a salt formed with a pharmaceutically suitable base thereof and one or more conventional carrier(s). The pharmaceutical combination is suitable for the prevention or treatment of, among others, diabetes mellitus.

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Duran et al. disclosed that cicletanine had a nephro-protective effect on the progression of renal disease in a hypertensive and diabetic rat model. Another result of the research was that treatment with cicletanine did not affect significantly hyperglycemia in animals [Duran, M.J. et al., European Heart Journal, 20, 422 (1999)].

Kohzuki et al. examined the renal and cardiac benefits of cicletanine and stated that the drug had a renal-protective effect. However, treatment with cicletanine did not improve diabetes in diabetic rats and did not affect urinary and blood glucose concentrations at the dose employed [Kohzuki, M. et al., Am. J. of Hypertension, 13, 298-306 (2000)].

Bringer et al. evaluated antihypertensive drugs to be administered to diabetic patients and stated that cicletanine used as monotherapy in moderated hypertension had the advantage not to interfere with the glycemic or lipid equilibrium [Bringer, J. et al., Revue Francaise d'Endocrinologie Clinique – Nutrition et Metabolisme 1992 France, 33, 337-345 (1992)].

Bayés et al. investigated the possible interaction between cicletanine and the hypoglycemic drug tolbutamide, however, no clinically relevant interaction was found [Bayés, M.C. et al., Eur. J. Clin. Pharm., 50, 381-384 (1996)].

Thus, it could be concluded that cicletanine did not have any influence on glycemia.

Claims:

1. A synergistic pharmaceutical combination suitable for the prevention or treatment of a prediabetic state, metabolic X-syndrome or type 2 diabetes mellitus as well as disorders which are associated with the states listed above, namely insulin resistance, dislipidemia and/or polycystic ovary syndrome comprising

(a) a first pharmaceutical composition containing cicletanine or a pharmaceutically suitable acid addition salt thereof and one or more conventional carrier(s), and

(b) a second pharmaceutical composition containing an antidiabetic or anti-hyperlipidemic active agent selected from the group consisting of metformin, troglitazone, glyburide or a pharmaceutically suitable acid addition salt thereof and lovastatin, and one or more conventional carrier(s).

2. A pharmaceutical combination of Claim 1 in which a single pharmaceutical composition comprises both the cicletanine or a pharmaceutically suitable acid addition salt thereof and the antidiabetic or anti-hyperlipidemic active agent or a pharmaceutically suitable acid addition salt thereof.

3. A pharmaceutical combination of Claim 1 or 2 comprising cicletanine or the hydrochloride thereof and metformin or a pharmaceutically suitable acid addition salt thereof.

4. A pharmaceutical combination of Claim 1 or 2 comprising cicletanine or the hydrochloride thereof and troglitazone.

5. A pharmaceutical combitanion of Claim 1 or 2 comprising cicletanine or the hydrochloride thereof and glyburide.

6. A pharmaceutical combitanion of Claim 1 or 2 comprising cicletanine or the hydrochloride thereof and lovastatin.

7. Use of cicletanine or a pharmaceutically suitable acid addition salt thereof for the preparation of a pharmaceutical composition to treat states related to hyperglycemia and/or insulin resistance, with the proviso that said states are other than diabetic nephropathy.

8. The use of Claim 7 in which the state is metabolic X-syndrome.

9. The use of Claim 6 in which the state is type 2 diabetes mellitus.

10. The use of Claim 6 in which the state is a prediabetic state.